Cover sheet

Title

Early postnatal (<96 hours) corticosteroids for preventing chronic lung disease in preterm infants

Reviewers

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Dates

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Contribution of reviewers

Intramural sources of support

Action Research UK Grant to study the effects of postnatal steroids, UK

Extramural sources of support

None

What's new

Two important follow-up studies have pointed to a 2-3 fold increased risk of abnormal neurological examination, cerebral palsy and developmental delay in preterm infants treated with early dexamethasone compared with controls. In addition, complications such as gastrointestinal bleeding, intestinal perforation, hyperglycaemia and hypertension are increased by early steroid treatment.

Dates

Date review re-formatted: 13/09/1999
Date new studies sought but none found: / /
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Text of review

Synopsis

Synopsis pending.

Abstract

Background

Chronic lung disease (CLD) remains a major problem in neonatal intensive care units. Persistent inflammation in the lungs is the most likely underlying pathogenesis. Corticosteroids have been used to either prevent or treat CLD because of their potent anti-inflammatory effects.

Objectives

To determine if postnatal corticosteroid treatment is of benefit in the prevention of chronic lung disease (CLD) in the preterm infant. This review examines the outcome of trials where preterm infants at risk of CLD were given postnatal steroids within 96 hours after birth.

Search strategy

Randomised controlled trials of postnatal corticosteroid therapy were sought from the Oxford Database of Perinatal Trials, the Cochrane Controlled Trials Register, Medline, hand searching paediatric and perinatal journals, examining previous review articles and information received from practising neonatologists.

Selection criteria

Randomised controlled trials of postnatal corticosteroid treatment within 96 hours of birth (early) in high risk preterm infants were selected for this review.

Data collection & analysis

Data regarding clinical outcomes including mortality, failure to extubate, pulmonary air leak, survival without chronic lung disease, CLD defined at 28 days postnatal age and 36 weeks post menstrual age, patent ductus arteriosus (PDA), severe intraventricular hemorrhage (IVH), infection, hyperglycaemia, hypertension, severe retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), gastrointestinal bleeding and longterm outcome were abstracted and analysed using Revman 4.0.4.

Main results

Fifteen randomised controlled trials of early postnatal corticosteroid treatment of preterm babies at risk of developing CLD were identified. A meta-analysis of these trials demonstrates benefits as regards earlier extubation, decreased risks of CLD at both 28 days and 36 weeks, death or CLD at 28 days, and PDA. There was an almost significant reduction in the risk of pulmonary air leak and in death or CLD at 36 weeks in the babies treated with early corticosteroids. There were no differences in the rates of neonatal mortality, infection, severe ROP, severe IVH, NEC and pulmonary haemorrhage. Gastrointestinal bleeding and intestinal perforation were important adverse effects and the risks of hyperglycaemia and hypertension were also increased. Several adverse neurological effects were found at follow-up examinations of survivors treated with early steroids: abnormal neurological examination, cerebral palsy and developmental delay.

Reviewers' conclusions

The benefits of early postnatal corticosteroid treatment (< 96 hours) may not outweigh the known or potential adverse effects of this treatment. Gastrointestinal effects early in the neonatal period and neurological effects seen at follow-up mean that current use of early postnatal steroids needs to be reconsidered. There is a compelling need for the long term follow-up and reporting of late outcomes, especially neurologic and developmental outcomes, among surviving infants who participated in all randomized trials of early postnatal corticosteroid treatment. The role of inhaled steroids remains to be elucidated.

Background

Surfactant therapy has improved the outcome of preterm infants with RDS, but the risk of chronic lung disease (CLD) or bronchopulmonary dysplasia (BPD) has been only modestly reduced (Egberts 1997). CLD and BPD are often used interchangeably and we have decided to use CLD to describe infants with oxygen dependency at either 28 days or 36 weeks in these three systematic reviews of postnatal corticosteroids. More babies with CLD are being cared for in neonatal units and their management is both time consuming and costly. Postnatal corticosteroid treatment has been shown to have some acute effects on lung function in babies with established CLD, especially those that are ventilator dependent (Mammel 1983; CDTG 1991). Recently there has been concern that the benefits of steroids might not outweigh the adverse effects which include hypertension, hyperglycaemia, intestinal perforation and extreme catabolism (Anonymous 1991; Ng 1993).

Even more recently corticosteroids have been used to try to prevent CLD by treating at risk preterm babies within the first three days of life (Yeh 1990; Sanders 1994). It is not clear if early use of steroids provides long-term benefits. Nor is it clear that adverse neurological outcomes found in animal studies do not apply to the immature human newborn infant.

In total, at least 30 randomized trials of postnatal steroids have been conducted in babies at risk of, or having CLD (see previous reviews by Halliday 1997; Halliday 1999; Arias-Camison 1999; Bhuta 1998; Doyle 1999 and an editorial by Tarnow-Mordi 1999). There are three existing Cochrane reviews, which review separately the trials in which postnatal steroids were started within 96 hours of birth, 7-14 days after birth, or after three weeks. This review examines the outcome of trials where preterm infants have been treated with corticosteroids within 96 hours of birth. It is an update of a previous review (Halliday 1997) and it includes outcome data from 4 additional trials.

Objectives

The objective of this overview is to examine the relative benefits and adverse effects of postnatal corticosteroids, administered within the first 96 hours of life to preterm infants at risk of developing CLD.

Criteria for considering studies for this review

Types of studies

Randomised controlled trials of postnatal corticosteroid therapy in preterm infants at risk of developing CLD, who were enrolled within 96 hours of birth (early).

Types of participants

Preterm babies at risk of developing CLD including those who are ventilator dependent.

Types of interventions

Intravenous corticosteroid versus control (placebo or nothing).

Types of outcome measures

Clinical outcome measures including mortality, survival without CLD, CLD defined at 28 days and 36 weeks, failure to extubate, pneumothorax, infection, hyperglycaemia, hypertension, severe ROP, PDA, severe IVH, NEC, gastrointestinal bleeding and longterm neuro-developmental outcomes in survivors.

Search strategy for identification of studies

Randomised trials of postnatal steroid therapy in preterm infants were sought from the Oxford Database of Perinatal Trials, the Cochrane Controlled Trials Register, Medline, hand searching of paediatric and perinatal journals, examination of review articles and information from practising neonatologists. Medline was searched from 1966 through January 2000 using the terms adrenal cortex hormones or dexamethasone or betamethasone or hydrocortisone, limits randomized controlled trials, human, all infant: birth - 23 months.

Methods of the review

For each trial information was sought regarding the method of randomisation, blinding, stratification, reporting of the outcome of all the infants enrolled and whether the trial was single or multicentered. Information on the trial participants included birthweight, gestational age, severity of RDS, need for mechanical ventilation and surfactant, and gender. Information on clinical outcomes was analysed for mortality, survival without CLD, CLD defined at 28 days and 36 weeks, failure to extubate, pneumothorax, infection, hyperglycaemia, hypertension, severe ROP, PDA, severe IVH, NEC, gastrointestinal bleeding and longterm outcomes. Meta-analysis of the included trials was performed using Revman 4.0.4.

Description of studies

Fifteen trials qualified for inclusion in this review. Most of the trials enrolled low birthweight babies with RDS, who were receiving mechanical ventilation.

The corticosteroid administered was usually dexamethasone and the commonest treatment regimen was 0.50 mg/kg/day for 3 days followed by 0.25 mg/kg/day for 3 days, 0.12 mg/kg/day for 3 days and 0.05 mg/kg/day for 3 days. There was, however, considerable variation. One study used hydrocortisone and the treatment regimens for dexamethasone included short courses of 1-2 days and longer courses of up to 4 weeks (see under Description of Studies).

The trial of Baden 1972 included 44 infants with respiratory distress syndrome, mild hypoxia and hypercapnia and a chest radiograph compatible with RDS. They were randomised to receive either hydrocortisone 15 mg/kg on admission and 12 hours later intravenously, or a placebo. Their birthweights ranged from 800 to 2805 g and gestational ages from 26 to 36 weeks.

The study of Yeh 1990 enrolled 57 infants whose birthweights were < 2000g and who had severe RDS based upon the appearances on a chest radiograph and the need for mechanical ventilation within four hours after birth. The absence of infection was also required for inclusion. The babies were randomly assigned to receive dexamethasone 0.50 mg/kg per dose every 12 hours from days 1-3, then 0.25 mg/kg per dose 12 hourly from days 4-6, then 0.12 mg/kg per dose 12 hourly from days 7 to 9 and finally 0.05 mg/kg per dose 12 hourly from days 10-12. All doses were given intravenously. A saline solution was used in the placebo group.

The study of Sanders 1994 enrolled 40 babies < 30 weeks' gestation who had RDS diagnosed by clinical and radiographic signs, required mechanical ventilation at 12-18 hours of age, and had received at least one dose of exogenous surfactant. Exclusion criteria at entry included a strong suspicion of sepsis or pneumonia, congenital heart disease, chromosome abnormalities and those infants who received an exchange transfusion. The babies were randomised to receive either dexamethasone 0.50 mg/kg between 12 and 18 hours of age and a second dose 12 hours later, or a saline placebo. Both treatments were given intravenously.

The study of Shinwell 1996 was a multicentre trial which randomised 248 infants of birthweight 500 to 2000 g if they had clinical and radiographic evidence of RDS, required mechanical ventilation in more than 40% oxygen, were less than 12 hours old and had no contraindications to steroid treatment, such as a bleeding tendency, hypertension, hyperglycaemia or active infection. Babies with lethal congenital

malformations were also excluded. The intervention group received dexamethasone 0.25 mg/kg intravenously every 12 hours for a total of six doses. The control group received intravenous saline.

The trial of Suske 1996 randomised 26 infants with gestational ages 24 to 34 weeks who had RDS that had been treated with surfactant. Infants with known septicaemia during the first week of life, haemodynamically relevant cardiac anomalies except for PDA, or malformations of the lung or CNS were excluded. Randomisation was by drawing lots prior to the age of two hours. The intervention group received dexamethasone 0.50 mg/kg intravenously in two divided doses for five days and the controls received no placebo.

The study of Rastogi 1996 recruited 70 infants with birthweights 700 to 1500 g who had severe RDS (assisted ventilation with 40% or more oxygen and/or 7 cmH2O mean airway pressure, a/A PO2 ratio of 0.24 or less) and had been treated with surfactant before entry. The infants were < 12 hours old. Infants were excluded if they had major malformations, chromosome abnormalities, 5 minute Apgar scores of < 3 or the presence of severe infection. The intervention group had dexamethasone intravenously every 12 hours according to the following schedule: 0.50 mg/kg/d on days 1-3, 0.30 mg/kg/d on days 4-6, 0.20 mg/kg/d on days 7-9 and finally 0.10 mg/kg/d on days 10-12. A saline placebo was given intravenously to the control group.

The study of Yeh 1997 was a multicentre randomised double-blind clinical trial of 262 preterm infants (< 2000 g) who had RDS and required mechanical ventilation from shortly after birth. The treated group had dexamethasone 0.25 mg/kg/dose every 12 hours i.v. from day 1 to 7; 0.12 mg/kg/dose every 12 hours i.v. from day 8 - 14; 0.05 mg/kg/dose every 12 hours i.v. from days 15 - 21; and 0.02 mg/kg/dose every 12 hours i.v. from day 22 to 28. Control infants had a saline placebo.

The study of Subhedar 1997 was a randomised trial which enrolled infants into one of four treatment groups using a factorial design. Both inhaled nitric oxide and early dexamethasone were compared separately with controls. 42 infants were randomised: 10 receiving inhaled NO alone; 11 dexamethasone alone; 10 both treatments; and 11 neither treatment. The 21 infants receiving dexamethasone were compared with 21 controls. Infants were eligible for entry into the trial at 96 hours of age if they met the following criteria: gestational age < 32 weeks, mechanical ventilation from birth, had received surfactant therapy and were thought to be at high risk of developing CLD using a scoring system (Ryan et al 1996). Exclusion criteria included major congenital anomaly, structural cardiac defect, significant ductus shunting, culture positive sepsis, IVH with parenchymal involvement, pulmonary or gastrointestinal haemorrhage, disordered coagulation or platelet count < 50,000. Dexamethasone was given intravenously at 12 hourly intervals for six days: 0.50 mg/kg/dose for six doses, and 0.25 mg/kg/dose for a further six doses. Control infants were not given a placebo.

The study of Sinkin 1998 was a multicentre randomised double-blind trial of 384 babies of less than 30 weeks' gestation with RDS. 189 babies received dexamethasone 0.50 mg/kg at 12 - 18 hours of age and with a second dose 12 hours later, and 195 babies had an equal volume of saline placebo.

The study of Kopelman 1999 was a prospective blinded randomised controlled trial of 70 babies of less than 28 weeks gestation who required mechanical ventilation. 37 infants received dexamethasone 0.20 mg/kg at delivery and 33 babies received a placebo of an equal volume of saline.

The study of Tapia 1998 was a multicentre double-blind placebo controlled trial of 109 preterm infants with RDS and birthweights between 700 and 1600 g who were treated with mechanical ventilation and surfactant. 55 babies were randomised to receive dexamethasone 0.50 mg/kg/day for 3 days, followed by

0.25 mg/kg/day for 3 days, followed by 0.12 mg/kg/day for 3 days and then 0.06 mg/kg/day for 3 days. 54 control infants received an equal volume of saline.

The study of Garland 1999 was a prospective multicentre randomised trial comparing a 3 day course of dexamethasone therapy beginning at 24-48 hours of life with placebo. 241 preterm infants (dexamethasone n=118, placebo n = 123) who weighed between 500 g and 1500 g, had received surfactant therapy and were at significant risk for CLD or death using a predictive model at 24 hours were enrolled. Dexamethasone was given in a 3 day tapering course at 12 hour intervals. The first 2 doses were 0.4 mg/kg, the 3rd and 4th doses were 0.2 mg/kg and the 5th and 6th doses were 0.1 mg/kg and 0.05 mg/kg respectively. A similar volume of normal saline was given to placebo treated infants at similar time intervals.

The study of Soll 1999 was a multicentre randomised double-blinded controlled trial comparing dexamethasone given at 12 hours of age with selective late dexamethasone therapy in premature infants weighing 501-1000 g (early dexamethasone n = 272, late selective therapy n = 270). The babies required assisted ventilation, had received surfactant therapy, were physiologically stable, had no obvious life threatening congenital anomaly, had blood cultures obtained and antibiotic therapy started. Infants were randomly assigned to early dexamethasone therapy or saline placebo. Intravenous dexamethasone was administered for 12 days according to the following schedule: 0.5 mg/kg/day for 3 days, 0.25 mg/kg/day for 3 days, 0.1 mg/kg/day for 3 days and 0.05 mg/kg/day for 3 days. Infants in either group could receive late postnatal steroids beginning on day 14 if they needed assisted ventilation with supplemental oxygen > 30%.

The study of Stark 1999 was a randomised multicentre controlled trial to compare a tapering course of stress dose corticosteroid started on the first day with placebo. Infants with birthweight 501 - 1000 g needing mechanical ventilation before 12 hours of age were eligible for the study. Infants with birthweight > 750 g also needed to have received surfactant and required an oxygen concentration of 30% or greater. The initial dose of dexamethasone was 0.15 mg/kg/day for 3 days, then tapered over 7 days. After enrolling 220 infants (sample size was 1200), the trial was halted for unanticipated adverse events. 111 infants had been randomised to receive dexamethasone and 109 placebo.

The study of Watterberg 1999 was a randomised double-masked placebo controlled pilot study to compare early treatment with low dose hydrocorticosone (1.0 mg/kg/day for 9 days, then 0.5 mg/kg/day for 3 days) begun before 48 hours of age with placebo. 40 infants weighing between 500-999 g and who were mechanically ventilated were enrolled at 2 centres, 20 hydrocortisone treated and 20 placebo controls.

Methodological quality of included studies

Baden 1972 - Randomisation was by vials and a table of random numbers. The clinical personnel were not aware of the content of any vial. Outcomes were given for all of the babies enrolled.

Yeh 1990 - Randomisation was performed in the pharmacy using balanced blocks of 10. The vials were labelled in the pharmacy and the clinical staff were unaware of the assignment. Sixty infants were included in the study and three were subsequently withdrawn: one because of death from Haemophilus influenzae septicaemia six hours after enrollment, and two because of an error in the measurement of birthweight (581 and 2200 g). Outcomes for these three infants are not given.

Sanders 1994 - Randomisation occurred in the pharmacy after opening a sealed envelopes. Dexamethasone or placebo were dispensed in labelled syringes. Clinical personnel were not aware of the assignment of the intervention. Outcomes are given for all 40 babies enrolled.

Shinwell 1996 - Each participating unit was supplied with numbered sets of syringes containing either dexamethasone or physiological saline. Syringes containing dexamethasone were not distinguishable from those containing saline. Syringe sets were numbered according to a random number list and randomisation was stratified by centre and by two birthweight groups: 500 - 1000 g and 1001 - 2000 g. The drug assignment was not known to any of the investigators until after the three month observation period of the last enrolled infant. Outcomes are reported for 248 of the 255 infants who were enrolled. The seven infants subsequently excluded from analysis included three with major congenital abnormalities (two with myotonic dystrophy and one with cyanotic congenital heart disease), three with errors in drug administration and one randomised after the age of 12 hours.

Suske 1996 - Randomisation was by drawing lots; the lot numbers corresponded to numbers on non-transparent envelopes. The random lots and the envelopes were drawn by a neutral, uninvolved person. The trial was considered as a pilot study before starting a multicentre study and it was planned that the trial would be stopped if a statistically significant difference was found between the groups. The inclusion criteria were met by 41 infants. Due to lack of cooperation and coordination at the beginning of the study, nine infants were not randomised. Four infants were excluded after randomisation because of definite signs of septicaemia. Results are given for 26 of the 28 remaining infants.

Rastogi 1996 - Randomisation occurred in the pharmacy using a random number list after stratifying for birthweight into three groups: 700-999 g, 1000 to 1249 g and 1250 g to 1500 g. The clinical team and other study personnel were blinded to the assignments until the study was completed and all outcome variables were recorded for all infants.

Yeh 1997 - The method of randomisation was by an assignment list in the central pharmacy. The sample size was calculated on the basis of an expected 50% reduction in the incidence of CLD with early dexamethasone, allowing a 5% chance of a type I error and a 10% chance of a type II error. Outcome data are presented for all 262 infants enrolled. The study is described as double-blind.

Subhedar 1997 - Randomised trial with factorial design providing four groups. Block randomisation was performed using computer generated random numbers and sealed envelopes. No placebo was used. There was no evidence of blinding of clinicians. Outcome measures were reported for all infants enrolled.

Sinkin 1998 - A multicentre randomised double-blind trial, but the method of randomisation was not described. Outcome data appear to have been provided for all infants enrolled.

Kopelman 1999 - This was a prospective blinded randomised controlled trial with randomisation performed in the pharmacy after stratification for treatment with antenatal steroids. The blinded clinical team provided care. Outcome data were provided for all infants enrolled.

Tapia 1998 - A multicentre double-blind placebo controlled study with random assignment at each centre using ampoules of dexamethasone and saline prepared in the hospital pharmacy of one of the centres. Outcomes were reported for 109 of the 113 infants enrolled. Two babies from the dexamethasone group were excluded, 1 because of congenital cystic adenomatoid malformation and 1 because of early sepsis. Two patients from the placebo group were excluded, 1 because of early sepsis and the other was transferred to another hospital at 2 weeks of age and further data on outcome could not be obtained.

Garland 1999 - A multicentre randomised controlled trial with infants randomised at each centre within each of 4 strata based on birthweight (< 1001 g, > 1000 g) and arterial/Alveolar (a/A) ratio before surfactant (< 0.16, > 0.15). Randomisation codes were maintained by the study pharmacists at each centre. Investigators, caregivers and parents were blinded to treatment allocation. At the first interim analysis (n=75), an increased risk of gastrointestinal perforation was noted in the dexamethasone group. After adjusting for severity of illness the difference was not of statistical significance to stop enrollment. However, to ensure patient safety the data monitoring committee recommended reducing the dexamethasone dose. The dosing schedule was changed to 4 doses of 0.25 mg/kg/dose every 12 hours begun at 24 to 48 hours, followed by doses of 0.125 mg/kg and 0.05 mg/kg at the next two 12 hour periods respectively. After the first interim analysis all enrolled infants received ranitidine therapy during the first 3 days of the study. Outcome measures appear to have been reported for all 241 infants enrolled in the study.

Soll 1999 - A multicentre randomised double blinded controlled trial with randomisation in hospital pharmacies after opening opaque sealed envelopes supplied by the Vermont Oxford Neonatal Network. The study was stopped prior to completion of sample size goals due to concern regarding adverse effects in the early steroid therapy group. Outcome measures appear to have been reported for most of the 542 infants enrolled.

Stark 1999 - A randomised multicentre controlled trial with random allocation performed in hospital pharmacies using random number scheme. The study had a factorial design so that infants were also randomised to routine ventilator management or a strategy of minimal ventilator support aimed at reducing mechanical lung injury. After enrolling 220 infants from a sample size estimate of 1200 the trial was halted for unanticipated adverse effects. Outcome measures seem to have been reported for all 220 patients enrolled in the trial.

Watterberg 1999 - A randomized double-masked placebo-controlled pilot study with infants randomised at each centre by constant block design with 4 patients per block to minimise bias over time. Separate randomisation tables were used for infants exposed to antenatal steroids. The hydrocortisone doses and the placebo of normal saline were prepared by the hospital pharmacies. Outcome measures were reported for all of the 40 infants enrolled in the trial.

Results

Baden 1972 - No significant effect on blood gases, pH, oxygen requirement, need for assisted ventilation or survival was demonstrated in this study.

Yeh 1990 - Infants in the dexamethasone group had significantly higher pulmonary compliance, tidal volume and minute ventilation, and required lower mean airway pressure for ventilation than infants in the placebo group. The endotracheal tube was successfully removed from more infants in the dexamethasone group (16/28 vs 8/29; $p < 0.025$) at two weeks of age. Nineteen infants (65%) in the placebo group and 11 (39%) in the dexamethasone group ($p < 0.05$) had lung injuries characterised by:

1. surviving infants with CLD
2. infants who died of intractable respiratory failure and had evidence of CLD at autopsy, and
3. infants who died of intractable respiratory failure with clinical evidence of CLD

Dexamethasone therapy was associated with a temporary increase in blood pressure and plasma glucose concentration and a delay in somatic growth.

Sanders 1994 - The dexamethasone group required less ventilatory support (mean airway, peak respiratory and end-expiratory pressures, and intermittent mandatory ventilation) and supplemental oxygen after study day 4 (all $p < 0.05$, repeated measures analysis of variance). Improved tidal volume in the dexamethasone group, as assessed by pulmonary function testing of infants who remained intubated, was seen on study day 7 ($p = 0.02$, t test). The dexamethasone group required a shorter time in hospital (median 95 days vs 106 days, $p = 0.01$, proportional hazards regression). Survival in the dexamethasone group was 89% vs 67% in the placebo group ($p = 0.08$, chi squared analysis). Survival without CLD was 68% in the dexamethasone vs 43% in the placebo group ($p = 0.14$). Mean blood pressure was elevated on study day 4 to 7. No differences in the rate of hyperglycaemia, incidence or severity of IVH, or days to regain birthweight were seen.

Shinwell 1996 - No differences were found in any outcome variable except for a reduction in the need for mechanical ventilation at three days in dexamethasone treated infants (54/122, 44% vs 71/106, 67%; $p = 0.001$). Gastrointestinal haemorrhage, hypertension and hyperglycaemia were more common in treated infants, but no life threatening complications, such as gastrointestinal perforation, were encountered. Follow-up of survivors at two to six years showed no evidence of effect on the incidence of moderate to severe neurologic impairment. However, there was a significant increase in the incidence of abnormal neurologic exam, and in developmental delay. There was a three-fold increase in the incidence of cerebral palsy in survivors, and a 1.6-fold increase in the combined outcome, death or cerebral palsy.

Suske 1996 - Infants in the dexamethasone group were extubated earlier (6.6 d vs 14.2 d; $p < 0.02$) and required less time in supplemental oxygen (4.2 d vs 12.5 d; $p < 0.02$); pulmonary complications tended to be lower in the dexamethasone group (1/14 vs 4/12), as was the frequency of retinopathy of prematurity (2/14 vs 6/12; $p < 0.05$).

Rastogi 1996 - Ventilator variables at 5-14 days were significantly improved in those infants who received dexamethasone compared to those who received placebo. The effect seemed to be more marked in infants weighing < 1250 g at birth. Significantly more infants could be extubated by 14 days in the dexamethasone group (26/32 vs 14/32; $p = 0.004$). Dexamethasone therapy reduced the incidence of CLD at 28 days (odds ratio, 0.10, 95% confidence interval, 0.03 - 0.30) and eliminated CLD at 36 weeks post-conceptional age. Dexamethasone treated infants had a greater weight loss at 14 days (12.9% vs 3.7%; $p = 0.01$) and higher blood pressures from days 3-10. However, no differences were seen in time to regain birthweight, hypertension (one infant in each group), or incidence of intraventricular haemorrhage.

Yeh 1997 - Infants in the dexamethasone group had a significantly lower incidence of CLD than those in the placebo group judged either at 28 postnatal days (21/132 vs 40/130, $p < 0.05$) or at 36 post-conceptional weeks (20/132 vs 37/130, $p < 0.05$). More infants in the dexamethasone group were extubated during the study. There was no difference between the groups for mortality (39/130 vs 44/132); however a higher proportion of infants in the dexamethasone group died in the late study period, probably attributable to infection. There was no difference between the groups for duration of oxygen therapy and hospitalisation. Significantly more infants in the dexamethasone group had either bacteraemia or clinical sepsis (44/132 vs 27/130, $p < 0.05$). Other immediate but transient side effects observed in the dexamethasone group were hyperglycaemia, hypertension, cardiac hypertrophy, hyperparathyroidism and delay in growth rate. Follow-up of survivors at two years corrected age showed no evidence of effect on moderate to severe neurologic impairment, or on the combined outcome, death or cerebral palsy. However, there was a significant increase in the incidence of abnormal neurologic exam, and a two-fold increase in cerebral palsy among survivors.

Subhedar 1997 - There was no difference in the combined incidence of CLD and/or death before discharge from hospital between either infants treated with dexamethasone and controls (RR 0.95, 95% CI 0.79-1.18) or those treated with inhaled NO and controls (RR 1.05, 95% CI 0.84-1.25).

Sinkin 1998 - No differences were found in the dexamethasone and placebo groups respectively for the primary outcomes of survival (79% vs 83%), survival without oxygen at 36 weeks corrected age (both 59%), and survival without oxygen at 36 weeks corrected age and without late steroids (46% vs 44%). No significant differences between the groups were found for median days in oxygen (50 vs 56 days), ventilation (20 vs 27 days), days to regain birthweight (15.5 vs 15.0 days), nor length or stay (88 vs 89 days). Babies given early dexamethasone were less likely to receive late steroids for BPD during their hospital stay (25 vs 35%, $p = 0.042$). No clinically significant side-effects were noted in the dexamethasone group although there were transient elevations in blood glucose and blood pressure with return to base-line by study day 10.

Kopelman 1999 - IMV rate and ventilation index improved more rapidly in the dexamethasone treated group. Mean blood pressure was higher after the first day in the dexamethasone group. Dexamethasone treated infants has fewer PDAs (13/37 vs 19/33; $p = 0.08$), and fewer received indomethacin (8/37 vs 15/33; $p = 0.03$). At the study hospital where early extubation was practised, more dexamethasone treated infants were extubated during the first week (10/22 vs 2/16, $p < 0.03$). There was no difference in IVH. No adverse effects occurred.

Tapia 1998 - There were no significant differences in mortality and/or CLD between the groups. There was a significant reduction in the number of infants requiring oxygen at 36 weeks postconception in the dexamethasone group (8% vs 33%; $p < 0.05$). Stepwise logistic regression analysis with oxygen dependency at 36 weeks postconception as the dependent variable and birthweight, gestational age, gender, prenatal steroids and study treatment as the independent variables showed that study treatment was the only variable significantly associated with oxygen dependency at 36 weeks. There were no differences in the number of days of mechanical ventilation and oxygen treatment between the groups. There were no differences in the incidences of major morbidity and possible complications related to steroid administration, except for a lower incidence of NEC in the dexamethasone group.

Garland 1999 - Early dexamethasone treated infants were more likely to survive without CLD (83/118 vs 71/123; $p = 0.03$) than placebo treated controls. There were also less likely to develop CLD if they survived to 28 days (16/99 vs 27/98; $p = 0.042$). Mortality rates were not significantly different. Subsequent dexamethasone therapy was used less often in the early dexamethasone treated infants who survived (68/99 vs 81/98; $p = 0.01$). Intestinal perforation was more common, but not significantly so, in the dexamethasone treated infants (12/118 vs 7/122; $p = 0.20$); during the first week of life the difference was significant (9/118 vs 1/122; $p = 0.009$). Babies in the dexamethasone group also spent less time in oxygen (median days 43 vs 50; $p = 0.04$). Any grade of PIVH (36% vs 52%; $p = 0.02$) and PDA ligation (14% vs 28%; $p = 0.01$) were also less common in the dexamethasone group. Hypertension and insulin therapy were needed more often in the dexamethasone treated infants ($p = 0.007$).

Soll 1999 - There were no differences in the primary outcome of CLD or death at 36 weeks adjusted age (early therapy 136/272 vs 143/270; $p = 0.50$). Infants who received early steroid therapy were less likely to need late treatment (114/272 vs 165/270; $p < 0.001$). They also had a lower risk of PDA; 92/272 vs 116/270; $p < 0.05$) and were less likely to receive indomethacin therapy (131/272 vs 178/270; $p < 0.001$). However, infants who received early steroid therapy were more likely to have complications such as gastrointestinal haemorrhage, (33/272 vs 19/270; $p < 0.05$), hyperglycaemia (201/272 vs 154/270; $p < 0.001$), and use of insulin therapy (169/272 vs 103/270; $p < 0.001$). There was a trend toward increased

gastrointestinal perforation (30/272 vs 19/270; $p < 0.01$). In infants who had cranial ultrasound scans there was an increase in PVL in the early steroid group (7% vs 3%; $p < 0.05$). Infants who received early steroid therapy had fewer days in supplemental oxygen but they experienced poorer weight gain.

Stark 1999 - The steroid treated infants had a lower incidence of the primary outcome, death or CLD at 36 post-menstrual weeks (63% vs 69%; $p < 0.05$). Fewer infants in the steroid group had pulmonary interstitial emphysema (9% vs 23%; $p < 0.05$), required oxygen at 28 days (78% vs 94%; $p < 0.05$) or had subsequent steroid treatment (34% vs 51%; $p < 0.05$). The rates of severe IVH, PVL, ROP and nosocomial infection were similar. Hypertension and hyperglycaemia were more frequent in the steroid group (27% vs 4% and 23% vs 12% respectively with both $p < 0.05$). During the first 14 days 14/111 (13%) infants in the steroid group and 3/109 (3%) infants in the placebo group had spontaneous gastrointestinal perforation without NEC ($p < 0.05$). Spontaneous perforation was also associated with indomethacin treatment ($p = 0.005$) and there was an interaction between indomethacin and steroid therapy ($p = 0.04$).

Watterberg 1999 - more infants treated with hydrocortisone survived without supplemental oxygen at 36 weeks post-conception (12/20 vs 7/20; $p = 0.023$). Hydrocortisone treatment was also associated with a reduction in duration of oxygen > 40% (7 vs 28 days; $p = 0.06$), duration of oxygen > 25% (48 vs 69 days; $p = 0.02$) and duration of mechanical ventilation (25 vs 32 days; $p = 0.03$). There were no differences in the rates of death, sepsis, PDA, NEC, gastrointestinal perforation, IVH or ROP.

Meta-analysis of these fifteen studies of early post-natal corticosteroid treatment shows no evidence of effect on neonatal mortality up to 28 days (typical relative risk, 1.08, 95% CI 0.88, 1.31), mortality before discharge (typical relative risk, 1.06, 95% CI 0.92, 1.23), infection (typical relative risk 1.02, 95% CI 0.85, 1.23), any ROP (typical relative risk 0.88, 95% CI 0.63, 1.21), severe IVH (typical relative risk 0.96, 95% CI 0.72, 1.26), necrotising enterocolitis (typical relative risk 0.88, 95% CI 0.62, 1.25) and pulmonary haemorrhage (typical relative risk 0.97, 95% CI 0.57, 1.63).

Significant benefits of early postnatal steroids were increased rate of weaning from ventilator demonstrated as failure to extubate by 3rd day (typical relative risk 0.68, 95% CI 0.55, 0.83; typical risk difference -0.21, 95% CI -0.32, -0.10), failure to extubate by 7th day (typical relative risk 0.72, 95% CI 0.59, 0.86; typical risk difference -0.14, 95% CI -0.21, -0.06) and failure to extubate by 14th day (typical relative risk 0.53, 95% CI 0.36, 0.78; typical risk difference -0.30, 95% CI -0.47, -0.14). Significant benefits also included reductions in CLD at 28 days (typical relative risk 0.79, 95% CI 0.70, 0.90; typical risk difference -0.09, 95% CI -0.14, -0.04), CLD at 36 wk (typical relative risk 0.68, 95% CI 0.56, 0.83; typical risk difference -0.08, 95% CI -0.11, -0.04), death or CLD at 28 days (typical relative risk 0.86, 95% CI 0.77, 0.95; typical risk difference -0.09, 95% CI -0.14, -0.03), death or CLD at 36 weeks (typical relative risk 0.89, 95% CI 0.81, 0.96, typical risk difference -0.06, 95% CI -0.09, -0.02), PDA (typical relative risk 0.67, 95% CI 0.58, 0.78; typical risk difference -0.12, 95% CI -0.16, -0.07) and pulmonary air leak (typical relative risk 0.52, 95% CI 0.35, 0.76); typical risk difference -0.07, 95% CI -0.10, -0.03). Infants who received steroids early were less likely to require later treatment (typical relative risk 0.72, 95% CI 0.64, 0.80; typical risk difference -0.14, 95% CI -0.18, -0.09).

Adverse effects included gastrointestinal bleeding (typical relative risk 1.88, 95% CI 1.34, 2.63; typical risk difference 0.06, 95% CI 0.03, 0.09), hyperglycaemia (typical relative risk 1.46, 95% CI 1.30, 1.64; typical risk difference 0.14, 95% CI 0.10, 0.18), hypertension (typical relative risk 1.79, 95% CI 1.49, 2.15; typical risk difference 0.12, 95% CI 0.09, 0.16) and intestinal perforation (typical relative risk 1.96, 95% CI 1.32, 2.92; typical risk difference 0.03, 95% CI 0.01, 0.05).

Only two of the 15 included trials have so far reported long-term follow-up results. The results from these two trials show no evidence of effect on Bayley MDI <70, Bayley PDI <70, abnormal EEG, moderate to severe neurologic impairment, or death or moderate to severe neurologic impairment. However, they show an increase in Bayley PDI < 70 in tested survivors (typical relative risk 1.74, 95% CI 1.02, 2.94; typical risk difference 0.17, 95% CI 0.01, 0.32); abnormal neurological exam (typical relative risk 2.46, 95% CI 1.59, 3.81; typical risk difference 0.14, 95% CI 0.08, 0.21; cerebral palsy (typical relative risk 2.32, (95% CI 1.48, 3.65; typical risk difference 0.12, 95% CI 0.06, 0.19; cerebral palsy in survivors (typical relative risk 2.61, (95% CI 1.74, 4.01); typical risk difference 0.25, 95% CI 0.15, 0.35); death or cerebral palsy (typical relative risk 1.35, 95% CI 1.11, 1.64; typical risk difference 0.14, 95% CI 0.05, 0.22); developmental delay (typical relative risk 1.68, 95% CI 1.08, 2.61; typical risk difference 0.14, 95% CI 0.03, 0.24); and an almost significant increase in moderate to severe neurologic impairment in survivors (typical relative risk 1.42, 95% CI 0.97, 2.08; typical risk difference 0.09, 95% CI -0.007, 0.19).

Discussion

Corticosteroids are powerful drugs which may improve lung function in infants with CLD by a number of different mechanisms. It has been suggested that they might have a role to play in the prevention of CLD by suppressing the inflammatory response in the lung of babies at risk (Groneck 1995). It has also been shown that babies who develop CLD have low cortisol levels following ACTH stimulation during the first week of life (Watterberg 1995). To be effective in preventing CLD corticosteroids may have to be given within the first few days of life.

This review has demonstrated that early corticosteroid treatment facilitates weaning from the ventilator. Additional advantages are increased survival without CLD at 28 days, reductions in the risk of CLD at both 28 days and 36 weeks post-conception, the need for late treatment with steroids, and PDA. On the other hand there are increases in the risk of gastrointestinal bleeding, intestinal perforation, hyperglycaemia and hypertension.

There are other potential hazards of corticosteroid treatment in the neonate including retardation of growth (Gibson 1993), protein breakdown (van Goudoever 1994), cardiac hypertrophy (Werner et al 1992) and possible adverse effects on development of the central nervous system (Weichsel 1977; Gramsbergen 1998) and lungs (Tschanz 1995). One study has shown a significant decline in the growth of head circumference with early corticosteroid treatment (Papile 1996). Longterm follow-up has been reported in two recent studies and the meta-analysis of these results show that early dexamethasone treatment is associated with a significant increase in the risk of abnormal neurological examinations, cerebral palsy and developmental delay with relative risks of about two to three for each of these outcomes. One of these studies was a four week tapering course of dexamethasone and so is similar to the six week tapering course of late steroids reported by O'Shea 1999 and included in the systematic review of delayed steroids. However, the yet to be published follow-up study of Shinwell et al (1999) (Shinwell 1996) reported adverse longterm neurological outcomes in children treated with only a three day course of early dexamethasone. This finding is of extreme importance and concern as there was about a three-fold increased risk of cerebral palsy in survivors and this included children with spastic diplegia, spastic quadriplegia and hemiplegia. Why dexamethasone given early for a short course should have such devastating effects is unknown. Certainly some infants would have been treated with repeat courses of dexamethasone but this would have been more likely in the control infants. Periventricular leukomalacia (PVL) is an obvious cause of cerebral palsy but studies have not shown a significant excess of this complication in steroid-treated infants compared with controls.

An important problem in interpreting the late follow-up data is that only two of the 15 trials of early postnatal steroids have reported late follow-up results; therefore, the possibility of follow-up bias and publication bias must be considered. A limitation of the two follow-up studies reviewed here is that only 82% of surviving infants were examined.

In a recent observational study of infants born after antenatal steroid therapy there appeared to be an excess of periventricular leukomalacia in those whose mothers had received dexamethasone rather than betamethasone (Baud 1999). Most studies of postnatal steroids have used dexamethasone in high doses of 0.5-1.0 mg/kg/day. Other steroids or lower doses of dexamethasone may prove to be safer. One study has suggested that low dose hydrocortisone has beneficial effects on the neonatal lung (Watterberg 1999). Further studies are needed comparing lower doses of steroids, other steroids and alternative routes of administration, e.g. by inhalation (see Cochrane Review by Shah 2000).

Reviewers' conclusions

Implications for practice

The benefits of early postnatal steroids in preterm infants at risk of developing CLD may not outweigh the real or potential adverse effects. Clinicians must decide if the reduction in CLD achieved at the increased risk of gastrointestinal bleeding, intestinal perforation, hyperglycaemia, hypertension and more importantly adverse longterm neurological outcome is justifiable. Clearly the current liberal use of postnatal steroids must be curtailed. Only infants who cannot be weaned from ventilation should be treated with these large doses of dexamethasone. This will preclude its use early (< 96 hours) in life.

Implications for research

There is a compelling need for the long term follow-up and reporting of late outcomes, especially neurologic and developmental outcomes, among surviving infants who participated in all randomized trials of early postnatal corticosteroid treatment. Tests of gross neurologic abnormality, cognitive functioning, and visual acuity should be included in these follow-up studies.

Future studies are needed concerning the accurate identification of those infants most at risk of developing CLD. Any future placebo-controlled trials of postnatal steroids in preterm infants should include long term neurologic follow-up. Studies comparing different doses and durations of corticosteroid treatment, and examining the effects of inhaled steroids, are urgently needed. Studies of potentially safer steroids such as hydrocortisone also need to be performed.

Acknowledgements

Potential conflict of interest

None

Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	All(
Baden 1972	Random allocation using random numbers and sealed envelopes. Blinding of randomisation: yes. Blinding of intervention: yes. Complete follow-up: yes. Blinding of outcome measurement: yes.	44 preterm infants < 24 hours old with respiratory distress both clinically and radiologically.	Hydrocortisone 25 mg/kg on admission and 12 hours later intravenously. Control group given placebo.	Death, FiO2, cortisol levels and blood gases.	The oldest study, carried out 1972 and the only one using hydrocortisone in a very short course of treatment.	A
Garland 1999	Randomisation by study pharmacists at each centre. Blinding of randomisation: yes. Complete follow-up: yes. Blinding of outcome measurements: yes.	241 infants weighing between 500 and 1500 g, received surfactant, at significant risk for CLD or death using a model to predict at 24 hours.	3 day course of dexamethasone beginning at 24-48 hours. The first 2 doses were 0.4 mg/kg, 3rd and 4th doses 0.2 mg/kg and the 5th and 6th doses 0.1 mg/kg and 0.05 mg/kg respectively. A similar volume of normal saline was given to control infants.	The primary outcomes were survival without CLD defined as oxygen therapy at 36 weeks to maintain SaO2 above 91% and mortality. Secondary outcomes included duration of ventilation and supplemental oxygen, respiratory support at 28 days, length of stay for survivors, use of subsequent dexamethasone therapy and usual complications of prematurity.	At the first interim analysis (n = 75) an increased risk of GI perforation was noted in the dexamethasone group. The data monitoring committee recommended reducing the dexamethasone dose to: 4 doses of 0.25 mg/kg/dose every 12 hours begun at 24 - 48 hours followed by doses of 0.125 mg/kg and 0.05 mg/kg at the next 2 12 hour periods respectively.	A
Kopelman	Random	70 infants of < 28	Dexamethasone	Ventilation Index	After an	A

1999	allocation in the hospital pharmacy stratified by use of antenatal steroids Blinding of randomisation: yes. Blinding of intervention: yes. Complete follow-up: yes. Blinding of outcome measurement: yes.	weeks gestation requiring intermittent mandatory ventilation and arterial catheterisation.	0.2 mg/kg within 2 hours of delivery. Control infants given an equal volume of saline.	(VI), IMV rate, mean blood pressure, incidence of PDA, need for indomethacin and number extubated during the first week and usual complications of RDS.	interim analysis showed that the incidence of IVH was much lower than expected, enrollment was stopped and the analysis was limited to a comparison of ventilator settings, blood pressure and pressor use during the first 7 days. The outcome of successful extubation was available at only one hospital were 38 infants were enrolled.	
Rastogi 1996	Random allocation: using a pharmacy list, stratified for birthweight. Blinding of randomisation: yes. Blinding of intervention: yes. Complete follow-up: yes. Blinding of outcome measurement: yes.	70 preterm infants < 12 h old, weighing 700 - 1500 g with RDS clinically and radiologically, babies needed mechanical ventilation > 30% O2 and / or MAP 7 cmH2O a/A < 0.25 after surfactant treatment. Exclusions for major malformations, chromosome abnormalities, severe infection, Apgar < 3 at 5	Intravenous dexamethasone 0.5 mg/kg/day for 3 days, 0.25 mg/kg/day for 3 days, 0.15 mg/kg/day for 3 days, 0.05 mg/kg/day for 3 days. Control group given saline placebo.	FiO2, MAP, BPD (28 days and CXR), severe BPD (36 weeks), duration O2, infections, deaths, PTX, PH, PDA, IVH, NEC, Hyperglycemia, insulin use, hypertension, ROP		A

		minutes				
Sanders 1994	Random allocation in the Pharmacy using sealed envelopes. Blinding of randomisation: yes. Blinding of intervention: yes. Complete follow-up: yes. Blinding of outcome measurement: yes.	40 babies < 30 weeks gestation and 12-18 hours old with RDS, both clinical and radiological. The babies were being treated with mechanical ventilation and surfactant and exclusions comprised sepsis, congenital heart disease, chromosome abnormalities or need for exchange transfusion.	Dexamethsone 0.5 mg/kg twice intravenously. Control group given saline placebo.	MAP, FiO2, mortality, extubation < 7 days, PFT, duration IPPV, O2, hospital, mortality, BPD (36 weeks O2), late steroids		A
Shinwell 1996	Random allocation, stratified by centre and birthweight, from random numbers list in Pharmacy. Blinding of randomisation: yes. Blinding of intervention: yes. Complete follow-up: yes for short term. 84% for long term. Blinding of outcome measurement: yes.	248 preterm babies with birthweight 500 - 2000 g, 1-3 days old, requiring mechanical ventilation with more than 40% oxygen. Exclusions for active bleeding, hypertension, hyperglycaemia, active infection and lethal congenital anomalies	Intravenous dexamethasone 0.25 mg/kg every 12 h six times. Controls given saline placebo.	Mortality, survival with no O2, MV3 and 7 days, CLD, duration hospital, IVH, PVL, RIO PTX PIE, PDA, sepsis, hypertension, hyperglycaemia		A
Sinkin 1998	Random allocation but method not described. Blinding of randomisation: yes. Blinding of	384 babies < 30 weeks' gestation with RDS.	Dexamethasone 0.5 mg/kg at 12-18 hours of age and second dose 12 hours later. Control group given an	Primary outcomes were survival, survival without oxygen at 36 weeks corrected age and survival without oxygen at 36 weeks	Paper published as an abstract so that information is incomplete.	A

	intervention: yes. Complete follow-up: yes. Blinding of outcome measurement: yes.		equal volume of placebo.	corrected age and without late steroids. Length of time in oxygen, on ventilation, to regain birthweight and in hospital.		
Soll 1999	Random allocation in hospital pharmacies by opening opaque sealed envelopes. Blinding of randomisation: yes. Blinding of intervention: yes. Complete follow-up: yes. Blinding of outcome measurement: yes.	542 infants weighing 501 - 1000 g who required assisted ventilation < 12 h, had received surfactant by 12 hours, were physiologically stable and had no life threatening congenital anomalies.	Dexamethasone 0.5 mg/kg/day for 3 days. 0.25 mg/kg /day for 3 days, 0.10 mg/kg/day for 3 days and 0.05 mg/kg/day for 3 days. Control infants received a similar volume of normal saline. Infants in either group could receive late post-natal steroids beginning on day 14 if they were on assisted ventilation with supplemental oxygen > 30%.	Primary outcome was CLD or death at 36 weeks adjusted age. Secondary outcome measures included clinical status at 14 days and 28 days, duration of assisted ventilation, supplemental oxygen and hospital stay, treatment with late postnatal steroids, proven sepsis, hypertension and hyperglycaemia requiring therapy, weight at 36 weeks and the usual complications of prematurity.	Published as an extended abstract and presented at a clinical meeting.	A
Stark 1999	Random allocation using random numbers list supplied to pharmacy, stratified by birth weight. Blinding of randomisation: yes. Blinding of intervention: yes. Complete follow-up: yes, blinding of outcome	220 infants with birthweight 501 - 1000 g mechanically ventilated < 12 h. Infants > 750 g also need to receive surfactant and have FiO2 > 0.29.	Dexamethasone 0.15 mg/kg/day for 3 days, then tapered over 7 days or saline placebo.	Death or CLD, oxygen at 28 d PIE, late steroid treatment, hypertension, hyperglycaemia, GI perforation.	Factorial design, infants also randomised to routine ventilator management or a strategy of minimal ventilator support to reduce mechanical lung injury. After enrolling 220 infants	A

	measurements: yes.				(sample size estimate was 1200) the trial was halted for unanticipated adverse events.	
Subhedar 1997	Random allocation by computer generated random numbers and sealed envelopes. Factorial design provided 4 groups: early dexamethasone, inhaled NO, both drugs together and neither drug. Blinding of randomisation: yes. Blinding of intervention: probably not. Complete follow-up: yes. Blinding of outcome measurements: probably not.	42 preterm babies, entry at 96 hours if gestation < 32 weeks, mechanical ventilation from birth, surfactant treatment and high risk of developing CLD by a score (Ryan et al 1996). Exclusion criteria: major congenital anomaly, structural cardiac defect, significant ductus shunting, culture positive sepsis, IVH with parenchymal involvement, pulmonary or gastrointestinal haemorrhage, abnormal coagulation, or thrombocytopenia (platelets < 50,000).	Intravenous dexamethasone at 12 hourly intervals for 6 days; 0.5 mg/kg/dose for 6 doses and 0.25 mg/kg/dose for a further 6 doses. Inhaled NO 5-20 ppm for 72 hours. Control groups were not given a placebo.	Mortality, CLD at 28 days and > 36 weeks with abnormal chest radiograph. Duration of ventilation, time to extubation, duration of hospitalisation, maximum grade of IVH, pulmonary haemorrhage, pneumothorax, severe PDA, NEC, stage III or IV ROP. Complications including ileal perforation, upper GI haemorrhage, hyperglycaemia, hypertension, septicaemia.	Note factorial design which means that half of the treated and half of the control infants also received 72 hours of inhaled NO.	A
Suske 1996	Random allocation using sealed envelopes. Blinding of randomisation: yes, blinding of intervention: probably not. Complete	26 preterm infants < 2 h old, with birthweight < 1500 g if FiO2 > 0.50, or > 1500 g birthweight with FiO2 0.70, exclusion for known sepsis, cardiac	Intravenous dexamethasone 0.5 mg/kg/day for 5 days. Controls were not given a placebo.	Blood gases, ventilator settings, mortality IVH, BPD (O2 28 days), NEC, late sepsis, PDA, ROP, air leak, duration hospital		A

	follow-up: yes. Blinding of outcome measurement: probably not.	anomalies, malformations of lung or CNS			
Tapia 1998	Random allocation using ampoules of dexamethasone and saline prepared in the hospital pharmacy. Blinding of randomisation: yes. Blinding of intervention: yes. Complete follow-up: almost (109/113). Blinding of outcome measurement: yes.	113 (4 exclusions for congenital abnormality, early sepsis and failure to obtain follow-up data) infants with birthweight between 700 and 1600 g, clinical and radiological diagnosis of RDS, needing mechanical ventilation and < 36 hours of age. Exclusion criteria were life-threatening congenital malformation or chromosome abnormality, a strong suspicion of infection at birth (maternal chorioamnionitis), or early sepsis (positive blood culture in the first 36 hours of life).	Intravenous dexamethasone 0.5 mg/kg/day for 3 days, 0.25 mg/kg for 3 days, 0.12 mg/kg/day for 3 days and 0.06 mg/kg/day for 3 days. The placebo group received an equivalent volume of saline solution.	The primary outcomes were death before hospital discharge, BPD (defined as oxygen need at 28 days and x-ray changes), death or BPD and oxygen need at 36 weeks. Other outcomes included time on ventilator, time in over 40% oxygen and time in oxygen. Major morbidity and complications included pneumothorax, PIE, PDA, pulmonary haemorrhage, pneumonia, sepsis, NEC, ROP, arterial hypertension, hyperglycaemia and IVH (grades I-II, and III-IV).	A
Watterberg 1999	Random allocation at each centre by constant block design with 4 patients per block to minimise bias over time. Separate randomisation tables were	40 infants weighing between 500 and 999 g who were appropriate for gestational age and needed mechanical ventilation < 48 hours of age. Exclusion criteria included maternal	Hydrocortisone 1.0 mg/kg/day every 12 hours for 9 days, 0.5 mg/kg/day for 3 days. Control infants were given an equal volume of normal saline.	The primary outcome was survival without supplemental oxygen at 36 weeks post conception. Secondary outcomes included in survivors; CLD at 36 weeks, duration of mechanical ventilation, > 40%	A

	used for infants exposed to antenatal steroids. Randomisation was probably performed in hospital pharmacies. Blinding of randomisation: yes. Blinding of intervention: yes. Complete follow-up: yes. Blinding of outcome measurement: yes.	diabetes, congenital sepsis and SGA.		oxygen, > 25% oxygen, hospital stay, and weight and head circumference at 36 weeks.		
Yeh 1990	Random allocation in blocks of ten using a Pharmacy list. Blinding of randomisation: yes. Blinding of intervention: yes. Complete follow-up: almost. Blinding of outcome measurements: yes.	57 preterm infants weighing between 700 and 1999 g, < 13 hours old with severe RDS both clinically and radiologically. They needed mechanical ventilation < 4 h and were excluded if they had infection.	Intravenous dexamethasone 0.5 mg/kg/day for 3 days, 0.25 mg/kg/day for 3 days, 0.12 mg/kg/day for 3 days, 0.05 mg/kg/day for 3 days. Control infants were given saline placebo.	MAP, FiO2, PFT, BP, glucose, mortality, CLD, duration O2, hospital, weight loss, sepsis, PDA, IVH > grade I, ROP		A
Yeh 1997	Random allocation by central pharmacy random number list. Blinding of randomisation: yes. Blinding of intervention: yes. Complete follow-up: Almost for short term.	262 babies of birthweight < 2000 g with RDS and requiring mechanical ventilation after birth.	Dexamethasone 0.25 mg/kg/dose every 12 hours intravenously on days 1-7; 0.12 mg/kg/dose every 12 hours intravenously from 8-14 days; 0.05 mg/kg/dose	Chronic lung disease either judged at 28 postnatal days or at 36 post-conceptional weeks. Extubation during the study, mortality, bacteraemia or clinical sepsis, and side effects of hyperglycaemia,		A

81% for long term. Blinding of outcome measurement: yes.		every 12 hours intravenously from day 15 to 21; and 0.02 mg/kg/dose every 12 hours intravenously from days 22 to 28. Control infants were given saline placebo.	hypertension, cardiac hypertrophy, hyperparathyroidism and growth failure.

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Table of comparisons

01 Early postnatal steroids (< 96 hours) vs control
- 01 Mortality (up to 28 days)
- 02 Mortality (before discharge)
- 03 Failure to extubate by 3rd day
- 04 Failure to extubate by 7th day
- 05 Failure to extubate by 14th day
- 06 Failure to extubate by 28th day
- 07 Death or CLD at 28 days
- 08 Death or CLD at 36 weeks
- 09 CLD (28 days)
- 10 CLD (36 weeks)
- 11 CLD at 36 weeks in survivors
- 12 Survivors discharged home on oxygen
- 13 Infection
- 14 Hyperglycaemia
- 15 Hypertension
- 16 Pulmonary air leak
- 17 PDA
- 18 Severe IVH
- 19 Severe IVH in infants examined
- 20 NEC
- 21 Gastrointestinal bleeding
- 22 Intestinal perforation
- 23 Pulmonary haemorrhage
- 24 PVL
- 25 PVL in infants with cranial ultrasound scans
- 26 PVL in survivors seen at follow-up
- 27 Received late steroids
- 28 Survivors who receive late steroids
- 29 Any ROP
- 30 Severe ROP
- 31 Severe ROP in survivors
- 32 Bayley MDI < 70
- 33 Bayley PDI < 70
- 34 Bayley MDI < 70 in tested survivors
- 35 Bayley PDI < 70 in tested survivors
- 36 Abnormal EEG
- 37 Abnormal EEG in tested survivors
- 38 Rehospitalisation in infancy
- 39 Rehospitalisation in infancy in survivors
- 40 Abnormal neurological exam

41 Abnormal neurological exam in tested survivors
42 Developmental delay
43 Developmental delay in tested survivors
44 Cerebral palsy
45 Death before follow-up in trials assessing cerebral palsy
46 Death or cerebral palsy
47 Cerebral palsy in tested survivors
48 Moderate to severe neurologic impairment
49 Death before follow-up in trials assessing neurologic impairment
50 Death or moderate to severe neurologic impairment
51 Moderate to severe neurologic impairment in survivors examined

Notes

Unpublished CRG notes

Short title (no longer in use): Postnatal corticosteroids (early)

Published notes

Amended sections

None selected

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Review: Early postnatal (<96 hours) corticosteroids for pr

Comparison or Outcome | Peto Odds Ratio (95%CI)

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